Paul Schulwitz

1279/03

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

Requestor's Name: Rebecca Cook (STIC) Serial Number: 09/445054

Date: 7/15/04 Phone: Rem 4C70 Art Unit: 1614

Sup. Neal Rosen

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Please provide structures for a) all compounds of claim 54 (L27)
b) paclitaxel (L4), taxane (L5), epothilone A (L6), epothilone B (L7), desoxyepothilone A (L8) desoxyepothilone B (L9). Use all of b) microtubule stabilizing agents.

Search prenyl-protein transferase inhibitor generically + all specific compounds of claim 54 + each compound of b to treat cancer.

for b) - only print 2 references for each - older than 6/4/98.

What is "stet histiocytic lymphoma, lung adenocarcinoma" (cl 49)

Thanks
Rebecca

STAFF USE ONLY

Date completed: _____
Searcher: _____
Terminal time: _____
Elapsed time: 60
CPU time: 135
Total time: _____
Number of Searches: _____
Number of Databases: _____

Search Site
_____ STIC
_____ CM-1
_____ Pre-S

Type of Search
_____ N.A. Sequence
_____ A.A. Sequence
_____ Structure
_____ Bibliographic

Vendors
_____ IG
1720.97 STN
_____ Dialog
_____ APS
_____ Geninfo
_____ SDC
_____ DARC/Questel
_____ Other

PTO-1590 (8-90)

Inventor Record w/ structures

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:804132 HCAPLUS
DOCUMENT NUMBER: 130:33009
ENTRY DATE: Entered STN: 23 Dec 1998
TITLE: A method of treating cancer using an antineoplastic agent-**prenyl**-protein transferase inhibitor combination, and compound preparation
INVENTOR(S): **Rosen, Neal**; Sepp-lorenzino, Laura; **Moasser, Mark M.**; Oliff, Allen I.; Gibbs, Jackson B.; Kohl, Nancy; Graham, Samuel L.; Prendergast, George C.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Sloan-Kettering Institute for Cancer Research
SOURCE: PCT Int. Appl., 379 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A01N043-50
SECONDARY: A01N043-60; A61K031-415; A61K031-495
CLASSIFICATION: 1-6 (Pharmacology)
Section cross-reference(s): 8, 34, 63
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9854966	A1	19981210	WO 1998-US8646	19980604
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9877957	A1	19981221	AU 1998-77957	19980604
EP 986302	A1	20000322	EP 1998-926029	19980604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002503249	T2	20020129	JP 1999-502409	19980604

PRIORITY APPLN. INFO.:
US 1997-48736P P 19970605
GB 1998-1231 A 19980121
WO 1998-US8646 W 19980604

ABSTRACT:
Methods are provided for treating cancer using a combination of a compound which is an antineoplastic agent and a compound which is a inhibitor of **prenyl**-protein transferase. The methods comprise administering to a mammal, either sequentially in any order or simultaneously, amts. of ≥2 therapeutic agents selected from a compound which is an antineoplastic agent and a compound which is an inhibitor or **prenyl**-protein transferase. The invention also relates to methods of preparing such compns.

SUPPL. TERM: **prenyl** protein transferase inhibitor antineoplasric agent combination prepn antitumor
INDEX TERM: Microtubule
(agents stabilizing or disrupting; antineoplastic agent-**prenyl**-protein transferase inhibitor combination

prenyl-protein transferase inhib. (generic)


```
=> d que
L29         1305 SEA FILE=HCAPLUS ABB=ON  PLU=ON  FARNESYLTRANSFERASE/CT(L)(INHI
                 B? OR ANTAG? OR BLOCK?)
L30       178659 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTITUMOR AGENTS+OLD/CT
L31          873 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 AND L30
L32          727 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 AND (BAC OR DMA OR PAC OR
                 PKT OR THU)/RL
L34          439 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32 AND P/DT
L35          288 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32 NOT L34
L38           81 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L35 NOT PY>1998
L39            9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L38 AND REVIEW/DT
L40            9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 AND L39


=> d l40 ibib abs hitind 1-9

L40  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1999:73866  HCAPLUS
DOCUMENT NUMBER:          130:276077
TITLE:                    An update on COX-2 and farnesyltransferase inhibitor
                          development
AUTHOR(S):                Rotella, David P.
CORPORATE SOURCE:         Bristol-Myers Squibb Pharmaceutical Research
                          Institute, Princeton, NJ, 08543, USA
SOURCE:                   Current Opinion in Drug Discovery & Development
                          (1998), 1(2), 165-174
                          CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER:                Current Drugs Ltd.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 56 refs. on medicinal chemical and anti-inflammatory and
     antitumor effects of COX-2 and ras-farnesyltransferase inhibitors.
CC   1-0 (Pharmacology)
     Section cross-reference(s): 27, 28
IT   Antitumor agents
     Drug design
     Farnesylation
     Medicinal chemistry
        (medicinal chemical and pharmacol. of COX-2 and farnesyltransferase
        inhibitors)
IT   39391-18-9P
     RL: ADV (Adverse effect, including toxicity); BAC (Biological
     activity or effector, except adverse); BSU (Biological study,
     unclassified); PRP (Properties); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (2, inhibitors; medicinal chemical and pharmacol. of COX-2 and
        farnesyltransferase inhibitors)
IT   39391-18-9P
     RL: ADV (Adverse effect, including toxicity); BAC (Biological
     activity or effector, except adverse); BSU (Biological study,
     unclassified); PRP (Properties); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (2, inhibitors; medicinal chemical and pharmacol. of COX-2 and
        farnesyltransferase inhibitors)
```

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:8364 HCAPLUS
DOCUMENT NUMBER: 130:60514
TITLE: Farnesyltransferase inhibitors. A new approach to the development of potential anticancer drugs
AUTHOR(S): Schlitzer, Martin
CORPORATE SOURCE: Inst. Pharmazeutische Chemie, Philipps-Univ., Marburg, D-35032, Germany
SOURCE: Pharmazie in Unserer Zeit (1998), 27(6), 278-288
CODEN: PHUZBI; ISSN: 0048-3664
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: German
AB A review is given with 39 refs. on farnesyltransferase inhibition as a new antitumor approach including the topics Ras signal transduction pathway, posttranslational modification of Ras proteins, farnesyltransferase, development of farnesyltransferase inhibitors.
CC 1-0 (Pharmacology)
IT **Antitumor agents**
Drug screening
Signal transduction, biological
(farnesyltransferase inhibitors, development of potential anticancer drugs)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:740006 HCAPLUS
DOCUMENT NUMBER: 129:325626
TITLE: Novel approaches in development for the treatment of pancreatic cancer
AUTHOR(S): Butera, James; Malachovsky, Martin; Rathore, Ritesh; Safran, Howard
CORPORATE SOURCE: Departments of Med., Brown Univ., Providence, RI, USA
SOURCE: Frontiers in Bioscience [Electronic Publication] (1998), 3, E226-E229
CODEN: FRBIF6
URL: http://www.bioscience.org/1998/v3/e/butera/e226-229.htm
PUBLISHER: Frontiers in Bioscience
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English
AB A review with 45 refs. Pancreatic adenocarcinomas are among the neoplasms most resistant to conventional chemotherapeutic agents. This has prompted intense investigations of novel noncytotoxic agents based on new understandings of the mol. pathobiol. of human malignancies. This review focuses on the potential uses of 3 new classes of agents: farnesyl transferase (FTPase) inhibitors, matrix metalloproteinase inhibitors (MMPIs) and antibodies to the HER-2/neu oncogene. When used as single agents, FTPase inhibitors and MMPIs may be cytostatic, helping to delay the growth of these cancers. All 3 classes of agents may have the greatest benefit when used in conjunction with traditional anticancer modalities. The biol. mechanisms of these agents are discussed.

CC 1-0 (Pharmacology)
IT **Antitumor agents**
Antitumor agents
(pancreas; novel approaches to development of)
IT Antibodies
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pancreatic cancer treatment with antibodies to HER-2/neu oncogene)
IT **131384-38-8**, Farnesyltransferase 141907-41-7, Matrix metalloproteinase
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**inhibitors**; pancreatic cancer treatment with)

L40 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:301907 HCAPLUS
DOCUMENT NUMBER: 129:62295
TITLE: Advances in the development of farnesyltransferase inhibitors: substrate recognition by protein farnesyltransferase
AUTHOR(S): Yang, Wenli; Villar, Keith Del; Urano, Jun; Mitsuzawa, Hiroshi; Tamanoi, Fuyuhiko
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA
SOURCE: Journal of Cellular Biochemistry (1998), Volume Date 1997, (Suppl. 27), 12-19
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 40 refs. A variety of compds. that show promise in cancer chemotherapy and chemoprevention have been identified as farnesyltransferase inhibitors. These can be classified into mainly two different types of inhibitors, farnesyl diphosphate competitors and CAAX peptidomimetics. The former type acts by competitively inhibiting farnesyltransferase with respect to one of the substrates, farnesyl diphosphate, whereas the latter type acts by mimicking the other substrate, the C-terminal CAAX motif of Ras protein. One example of a farnesyl diphosphate competitor is manumycin, an antibiotic detected in the culture media of a Streptomyces strain. The CAAX peptidomimetics were developed based on the unique property of farnesyltransferase to recognize the CAAX motif at the C-terminus of the protein substrate. The authors recent studies have focused on understanding the structural basis of this CAAX recognition. By using in vitro mutagenesis, residues of yeast farnesyltransferase important for the recognition of the CAAX motif have been identified. Two of these residues are closely located at the C-terminal region of the β-subunit of farnesyltransferase. These and other results on the structural basis of the CAAX recognition may provide information valuable for structure-based design of farnesyltransferase inhibitors.
CC 1-0 (Pharmacology)
IT **Antitumor agents**
Drug design
Farnesylation

Peptidomimetics
(advances in the development of farnesyltransferase inhibitors)
IT 52665-74-4, Manumycin A 141400-83-1, SCH44342 156511-34-1, L 739749
157479-39-5, B 581 170006-72-1, FTI-276
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(advances in the development of farnesyltransferase inhibitors)
IT 13058-04-3, Farnesyl diphosphate
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(competitors; advances in the development of farnesyltransferase inhibitors)
IT 13058-04-3, Farnesyl diphosphate
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(competitors; advances in the development of farnesyltransferase inhibitors)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:403757 HCAPLUS
DOCUMENT NUMBER: 127:130255
TITLE: Inhibition of Ras prenylation: a signaling target for novel anti-cancer drug design
AUTHOR(S): Lerner, Edwina C.; Hamilton, Andrew D.; Sebti, Said M.
CORPORATE SOURCE: H. Lee Moffitt Cancer Center, Drug Discovery Program, Department of Biochemistry and Molecular Biology, University of South Florida, Tampa, FL, 33612, USA
SOURCE: Anti-Cancer Drug Design (1997), 12(4), 229-238
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 55 refs. The cancer-causing activity of Ras requires the prenylation of a cysteine fourth from its carboxyl terminus. Rational design of peptidomimetics of the carboxyl terminal tetrapeptide prenylation site on Ras resulted in pharmacol. agents capable of inhibiting Ras process, selectively antagonizing oncogenic signaling and suppressing human tumor growth in mouse models without side effects. This mini-review describes the efforts of several groups to design, synthesize and evaluate the biol. activities of farnesyltransferase and geranylgeranyltransferase I inhibitors. Among the important issues that will be discussed are the mechanism of action of these inhibitors and the potential mechanisms of resistance to inhibition of K-Ras farnesylation.
CC 1-0 (Pharmacology)
IT **Antitumor agents**
Drug design
(drug design of Ras prenylation inhibiting anticancer agents)
IT 135371-29-8, Geranylgeranyltransferase I
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(I; drug design of Ras prenylation inhibiting anticancer agents)
IT 135371-29-8, Geranylgeranyltransferase I
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(I; drug design of Ras prenylation inhibiting anticancer agents)

L40 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:44904 HCAPLUS
DOCUMENT NUMBER: 126:139314
TITLE: Oncologic, endocrine & metabolic. Farnesyl-protein transferase inhibitors in early development
AUTHOR(S): Singh, Sheo B.; Lingham, Russel B.
CORPORATE SOURCE: Merck and Co., Inc., Rathway, NJ, 07065, USA
SOURCE: Expert Opinion on Investigational Drugs (1996), 5(12), 1589-1599
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 47 refs. Over the last decade the underlying mechanisms that cause tumorigenesis are progressively being elucidated. One potential mechanism includes the participation of farnesyl-protein transferase in promoting the effects of oncogenic forms of ras. Membrane localization of Ras is essential for ras-induced tumor formation. Farnesyl-protein transferase catalyzes the attachment of farnesyl to the carboxyl terminal cysteine residue of Ras. Genetic evidence indicates that unprenylated oncogenic Ras is soluble, cannot promote tumorigenesis and is apparently not deleterious to the cell. Several inhibitors of farnesyl-protein transferase are currently being tested in animal models of tumorigenesis. This review will focus on compds. that are presently being developed by Eisai, Banyu, Bristol-Myers Squibb, Merck, Roche/Genentech/University of Texas, Schering-Plough and the University of Pittsburgh.
CC 1-0 (Pharmacology)
IT **Antitumor agents**
Transformation, neoplastic
(development of farnesyl-protein transferase inhibitors for inhibition of tumorigenesis in relation to to Ras)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:570368 HCAPLUS
DOCUMENT NUMBER: 125:265162
TITLE: Farnesyltransferase inhibitors: a new class of cancer chemotherapeutics
AUTHOR(S): Koblan, K. S.; Kohl, N. E.; Omer, C. A.; Anthony, N. J.; conner, M. W.; deSolms, S. J.; Williams, T. M.; Graham, S. L.; Hartman, G. D.; et al.
CORPORATE SOURCE: Departments of Cancer Research, Medicinal Chemistry and Safety Assessment, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Biochemical Society Transactions (1996), 24(3), 688-692
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB Peptidomimetic farnesyltransferase inhibitors such as L-739,749 are a new class of cancer chemotherapeutic drugs that act by inhibiting function of oncogenic Ras protein. A review on the subject is also given; 26 refs.

CC 1-6 (Pharmacology)
IT **Neoplasm inhibitors**
(peptidomimetic cancer chemotherapeutic drugs as farnesyltransferase inhibitors)
IT 156511-34-1, L 739749 160141-09-3, L744832
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(peptidomimetic cancer chemotherapeutic drugs as farnesyltransferase inhibitors)
IT 156511-34-1, L 739749 160141-09-3, L744832
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(peptidomimetic cancer chemotherapeutic drugs as farnesyltransferase inhibitors)

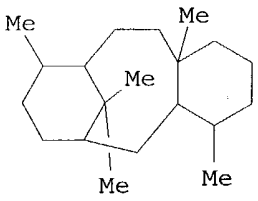
L40 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:160722 HCAPLUS
DOCUMENT NUMBER: 124:249420
TITLE: Farnesyltransferase inhibitors and anti-Ras therapy
AUTHOR(S): Gibbs, Jackson B.; Kohl, Nancy E.; Koblan, Kenneth S.; Omer, Charles A.; Sepp-Lorenzino, Laura; Rosen, Neal; Anthony, Neville J.; Conner, Michael W.; DeSolms, S. Jane; et al.
CORPORATE SOURCE: Department Cancer Research, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Breast Cancer Research and Treatment (1996), 38(1), 75-83
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 29 refs. The oncoprotein encoded by mutant ras genes is initially synthesized as a cytoplasmic precursor which requires post-translational processing to attain biol. activity; farnesylation of the cysteine residue present in the CaaX motif located at the carboxy-terminus of all Ras proteins is the critical modification. Once farnesylated and further modified, the mature Ras protein is inserted into the cell's plasma membrane where it participates in the signal transduction pathways that control cell growth and differentiation. The farnesylation reaction that modifies Ras and other cellular proteins having an appropriate CaaX motif is catalyzed by a housekeeping enzyme termed farnesyl-protein transferase (FPTase). Inhibitors of this enzyme have been prepared by several labs. in an effort to identify compds. that would block Ras-induced cell transformation and thereby function as Ras-specific anticancer agents. A variety of natural products and synthetic organic compds. were found to block farnesylation of Ras proteins in vitro. Some of these compds. exhibit antiproliferative activity in cell culture, block the morphol. alterations associated with Ras-transformation, and can block the growth of Ras-transformed cell lines in tumor colony-forming assays. By contrast, these compds. do not affect the growth or morphol. of cells transformed by the Raf or Mos oncoproteins, which do not require farnesylation to achieve biol. activity. The efficacy and lack of toxicity observed with FPTase inhibitors in an animal tumor model suggest that specific FPTase inhibitors may be useful for the treatment of some types of cancer.

CC 1-0 (Pharmacology)
IT **Neoplasm inhibitors**
(farnesyltransferase inhibitors and treatment of ras-dependent cancers)

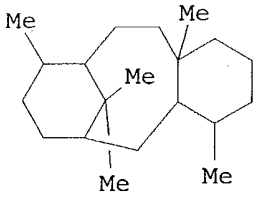
L40 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:47215 HCAPLUS
DOCUMENT NUMBER: 124:105390
TITLE: Inhibitors of protein farnesylation: A new approach to cancer chemotherapy
AUTHOR(S): Graham, Samuel L.
CORPORATE SOURCE: Department Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Expert Opinion on Therapeutic Patents (1995), 5(12), 1269-85
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 121 refs., of the types of compds. that are reported to inhibit the enzyme protein farnesyltransferase and the biol. effects of these compds. in vitro and in vivo. Topics discussed were: analogs of the protein substrate (CaaX mimetics); analogs of farnesyl diphosphate (FPP mimetics); bisubstrate analogs; and non-competitive inhibitors and inhibitors of unreported mechanism. The antitumor activity of these compds. centers around the interference with mutant oncogenic Ras proteins.
CC 1-0 (Pharmacology)
IT **Neoplasm inhibitors**
(protein farnesylation inhibitors in cancer chemotherapy)
IT **Neoplasm inhibitors**
(protein farnesylation inhibitors in cancer chemotherapy)

```
=> d que
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  TAXANE/CN
L30       178659 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTITUMOR AGENTS+OLD/CT
L64          125 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL AND L30
L65            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L64 AND REVIEW/DT NOT PY>1997


=> d 165 ibib abs hitind hitstr 1-5

L65  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1997:669181 HCAPLUS
DOCUMENT NUMBER:          127:287554
TITLE:                    Clinical overview of the taxanes
AUTHOR(S):                Goldspiel, Barry R.
CORPORATE SOURCE:         National Institutes of Health, Bethesda, MD,
                          20892-1196, USA
SOURCE:                   Pharmacotherapy (1997), 17(5, Pt. 2), 110S-125S
                          CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER:                Pharmacotherapy Publications
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 156 refs. Paclitaxel and docetaxel are taxane antineoplastic
     agents with broad antitumor activity. Since being introduced, they have
     become increasingly important in the treatment of a number of major solid
     tumors. Paclitaxel plus a Pt analog is now considered 1st-line therapy
     for advanced ovarian cancer, and both paclitaxel and docetaxel have
     significant activity as single agents in recurrent ovarian cancer.
     Docetaxel may be useful in some of these women with ovarian cancer who
     fail to progress after paclitaxel-containing treatments. Both drugs give
     significant response rates in the treatment of breast cancer and are
     options for patients with advanced disease, including anthracycline-
     refractory disease. Administration of taxanes in new combination regimens
     and as adjuvant therapy for breast cancer is under investigation; for
     example, the combination of paclitaxel and doxorubicin is highly active,
     and comparative studies of taxanes and anthracyclines should help clarify
     optimal treatment regimens in breast cancer. Both drugs have significant
     activity alone in the treatment of advanced non-small-cell lung cancer
     (NSCLC) and head and neck cancers. For the former, paclitaxel-cisplatin
     is now standard treatment in cooperative group combination therapy trials. As
     a result of its radiosensitizing properties, paclitaxel is undergoing
     extensive evaluation as combined modality treatment for advanced NSCLC and
     head and neck cancer. Both taxanes will probably be useful in combination
     regimens in head and neck cancer.
CC   1-0 (Pharmacology)
IT   Antitumor agents
        (clin. overview of the taxanes as)
IT   1605-68-1D, Taxane, derivs.  33069-62-4, Paclitaxel
     114977-28-5, Docetaxel
     RL: BAC (Biological activity or effector, except adverse); BSU
     (Biological study, unclassified); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (clin. antitumor effect of)
IT   1605-68-1D, Taxane, derivs.
     RL: BAC (Biological activity or effector, except adverse); BSU
```

(Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(clin. antitumor effect of)
RN 1605-68-1 HCAPLUS
CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, (4R,4aR,6S,9R,10S,12aR)- (9CI) (CA INDEX NAME)



L65 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:764215 HCAPLUS
DOCUMENT NUMBER: 123:159932
TITLE: Preclinical antitumor activity of taxanes
AUTHOR(S): Rose, William C.
CORPORATE SOURCE: USA
SOURCE: Taxol: Science and Applications (1995), 209-35. Editor(s): Suffness, Matthew. CRC: Boca Raton, Fla. CODEN: 61PEAY
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review with 70 refs. In vitro and in vivo activities of taxol and taxotere and taxanes are discussed.
CC 1-0 (Pharmacology)
IT **Neoplasm inhibitors**
(preclin. antitumor activity of taxanes)
IT **1605-68-1D**, Taxane, derivs. 33069-62-4, Taxol
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(preclin. antitumor activity of taxanes)
IT **1605-68-1D**, Taxane, derivs.
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(preclin. antitumor activity of taxanes)
RN 1605-68-1 HCAPLUS
CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, (4R,4aR,6S,9R,10S,12aR)- (9CI) (CA INDEX NAME)



L65 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:280269 HCAPLUS
DOCUMENT NUMBER: 122:106132
TITLE: Syntheses and structure-activity relationships of new taxoids
AUTHOR(S): Ojima, Iwao; Park, Young Hoon; Fenoglio, Ivana; Duclos, Olivier; Sun, Chung-Ming; Kuduk, Scott D.; Zucco, Martine; Appendino, Giovanni; Pera, Paula; et al.
CORPORATE SOURCE: Dep. Chem., State Univ. New York, Stony Brook, NY, 11794-3400, USA
SOURCE: ACS Symposium Series (1995), 583(Taxane Anticancer Agents), 262-75
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB Review with 34 refs. A series of new taxoids are synthesized from 14β-hydroxy-10-deacetylbaccatin III (14-OH-DAB). These new taxanes possess strong cytotoxicities against human cancer cell lines, and at least one of them possesses excellent antitumor activity in vivo. Pseudo-taxoids bearing N-acylphenylisoserine side chain at C-14 are synthesized, which are less active, but retain a certain level of cytotoxicity. Novel nor-seco-paclitaxel and docetaxel analogs are synthesized, which retain a certain level of activity despite the destruction of the A ring. New analogs bearing cyclohexyl groups at the C-3' and/or C-2 positions are synthesized and their cytotoxicity examined The results clearly indicate that Ph group at C-3' or C-2 is not a requisite for biol. activity. 3'-Isobutenyl and 3'-iso-Bu analogs of docetaxel show excellent activity against a drug-resistant cancer cell lines.

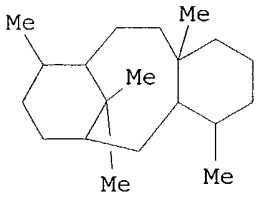
CC 30-0 (Terpenes and Terpenoids)
Section cross-reference(s): 1

IT **Neoplasm inhibitors**
(syntheses and structure-activity relationships of new taxoids)

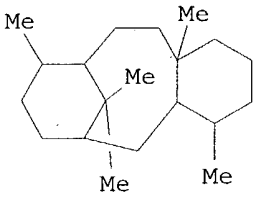
IT **1605-68-1DP**, Taxane, derivs.
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(syntheses and structure-activity relationships of new taxoids)

IT **1605-68-1DP**, Taxane, derivs.
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(syntheses and structure-activity relationships of new taxoids)

RN 1605-68-1 HCAPLUS
CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, (4R,4aR,6S,9R,10S,12aR)- (9CI) (CA INDEX NAME)



L65 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:569469 HCAPLUS
DOCUMENT NUMBER: 121:169469
TITLE: Paclitaxel and docetaxel: new anticancer agents
AUTHOR(S): Madelaine, I.; Faure, P.
CORPORATE SOURCE: Hop. Saint-Louis, Paris, 75010, Fr.
SOURCE: Journal de Pharmacie Clinique (1994), 13(1), 9-16
CODEN: JPCLDE; ISSN: 0291-1981
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: French
AB A review, with 57 refs. on taxanes as new anticancer agents.
CC 1-0 (Pharmacology)
IT **Neoplasm inhibitors**
(taxanes)
IT **1605-68-1D**, Taxane, derivs.
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of)
IT **1605-68-1D**, Taxane, derivs.
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of)
RN 1605-68-1 HCAPLUS
CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, (4R,4aR,6S,9R,10S,12aR)- (9CI) (CA INDEX NAME)



L65 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:498892 HCAPLUS
DOCUMENT NUMBER: 121:98892
TITLE: Taxoids: a new class of cytotoxic agents
AUTHOR(S): Marty, M.; Extra, J M.; Giacchetti, S.; Cuvier, C.; Espie, M.
CORPORATE SOURCE: Serv. d'Oncologie Med., Hop. St. Louis, Paris, F-75010, Fr.

SOURCE: Nouvelle Revue Francaise d'Hematologie (1994), 36(SUPPL. 1), S25-S28
CODEN: NRFHA4; ISSN: 0029-4810
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 17 refs., of the antitumor pharmacol. of the taxoids paclitaxel and docetaxel.

CC 1-0 (Pharmacology)

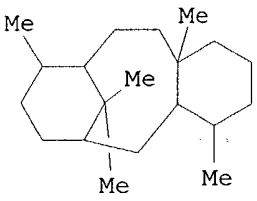
IT **Neoplasm inhibitors**
(taxoids paclitaxel and docetaxel as)

IT **1605-68-1D**, Taxane, derivs. 33069-62-4, Paclitaxel 114977-28-5, Docetaxel
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(neoplasm inhibition by)

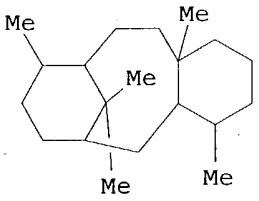
IT **1605-68-1D**, Taxane, derivs.
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(neoplasm inhibition by)

RN 1605-68-1 HCAPLUS

CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, (4R,4aR,6S,9R,10S,12aR)- (9CI) (CA INDEX NAME)



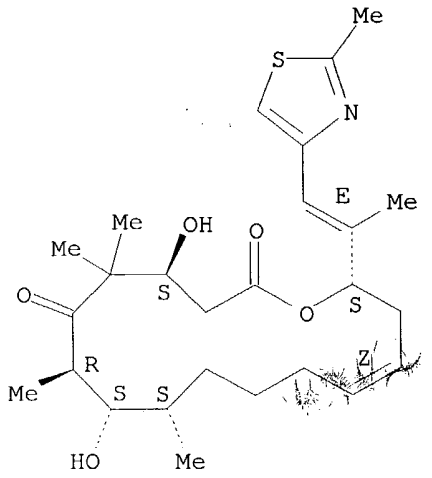
L27 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 1605-68-1 REGISTRY
CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, (4R,4aR,6S,9R,10S,12aR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6,10-Methanobenzocyclodecene, tetradecahydro-4,9,12a,13,13-pentamethyl-, [4R-(4α,4aβ,6α,9α,10α,12aα)]-
CN **Taxane (7CI, 8CI)**
OTHER NAMES:
CN Taxan
MF C20 H36
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CBNB, CEN, CIN, MEDLINE, PIRA, PROMT, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

273 REFERENCES IN FILE CA (1907 TO DATE)
147 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
273 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

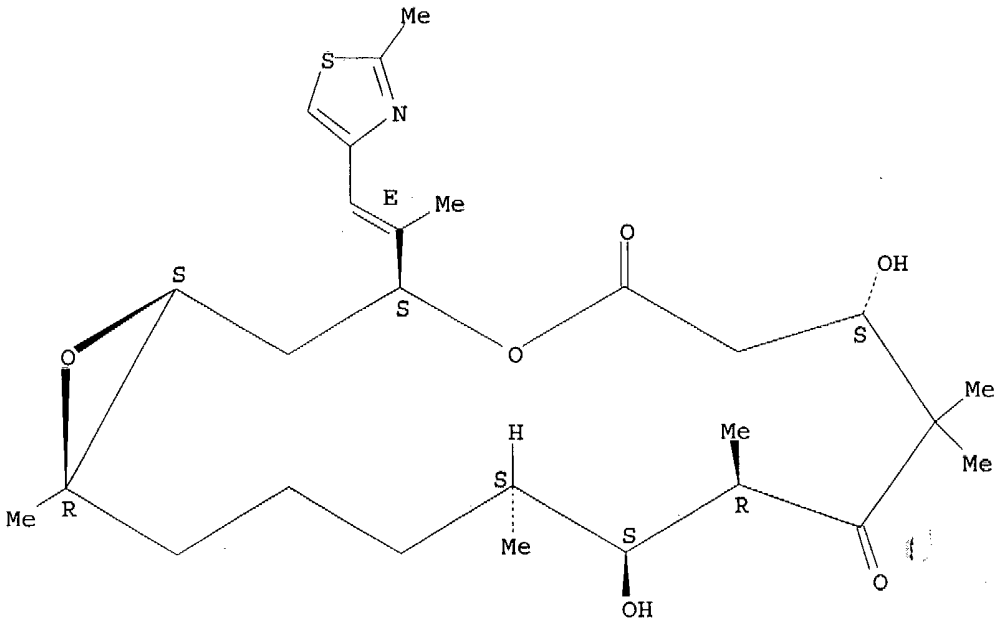
```
=> d que
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DESOXYEPOTHILONE A/CN
L30       178659 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTITUMOR AGENTS+OLD/CT
L70           41 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL AND L30
L71            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L70 AND REVIEW/DT NOT PY>1997


=> d l71 ibib abs hitind hitstr

L71  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1998:729  HCAPLUS
DOCUMENT NUMBER:          128:88685
TITLE:                    Metathesis vs metastasis: the chemistry and biology of
                          the epothilones
AUTHOR(S):                Finlay, Ray
CORPORATE SOURCE:         Dep. Chemistry, The Skaggs Inst. for Chemical Biol.,
                          The Scripps Res. Inst., La Jolls, CA, 92037, USA
SOURCE:                   Chemistry & Industry (London) (1997), (24), 991-996
                          CODEN: CHINAG; ISSN: 0009-3068
PUBLISHER:                Society of Chemical Industry
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 15 refs. on a recent entry onto the scene of potentially
     useful natural products, the epothilones A - E, providing valuable
     information for the fight against cancer via their interaction with
     microtubules.
CC   26-0 (Biomolecules and Their Synthetic Analogs)
     Section cross-reference(s): 1
IT   Antitumor agents
     Stereoselective synthesis
        (chemical and bioactivity of the epothilones)
IT   Antitumor agents
        (metastasis; chemical and bioactivity of the epothilones)
IT   152044-53-6P, Epothilone A   152044-54-7P, Epothilone B
     186692-73-9P, Epothilone C   189453-10-9P, Epothilone D
     201049-37-8P
     RL: BAC (Biological activity or effector, except adverse); BOC
     (Biological occurrence); BSU (Biological study, unclassified); SPN
     (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
     study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
        (chemical and bioactivity of the epothilones)
IT   186692-73-9P, Epothilone C
     RL: BAC (Biological activity or effector, except adverse); BOC
     (Biological occurrence); BSU (Biological study, unclassified); SPN
     (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
     study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
        (chemical and bioactivity of the epothilones)
RN   186692-73-9  HCAPLUS
CN   Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
     [(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
     (9CI)  (CA INDEX NAME)

Absolute stereochemistry.  Rotation (-).
Double bond geometry as shown.
```



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 152044-54-7 REGISTRY
CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-
OTHER NAMES:
CN (-)-Epothilone B
CN EPO 906
CN **Epothilone B**
CN Patupilone
FS STEREOSEARCH
MF C27 H41 N O6 S
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CIN, EMBASE, IMSRESEARCH, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

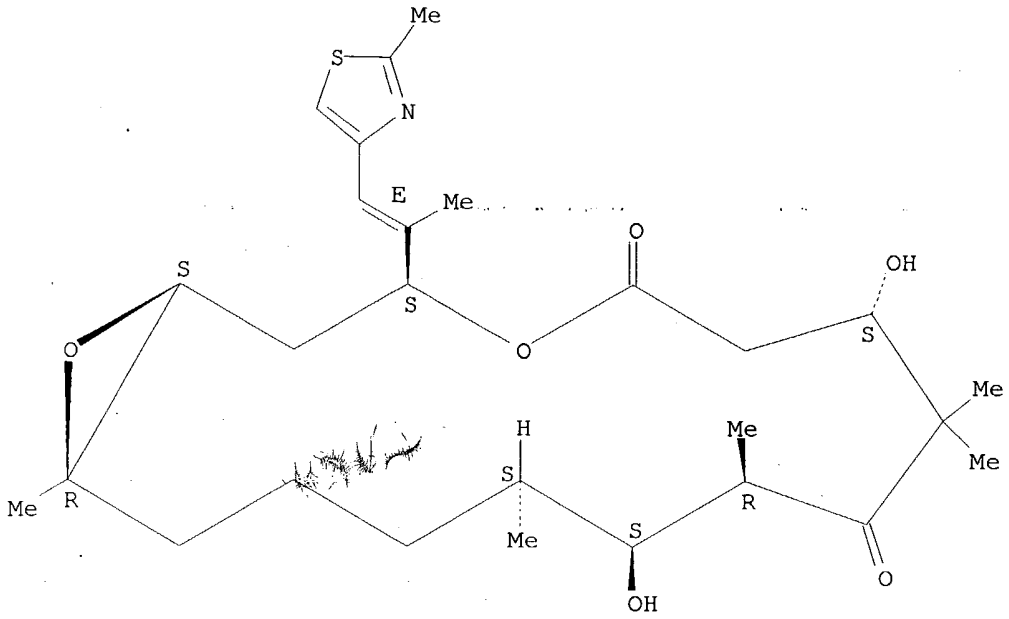
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

302 REFERENCES IN FILE CA (1907 TO DATE)
30 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
302 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> d que l69
L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  EPOTHILONE B/CN
L30       178659 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTITUMOR AGENTS+OLD/CT
L68          134 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL AND L30
L69            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L68 AND REVIEW/DT NOT PY>1997


=> d l69 ibib abs hitind hitstr 1-2

L69  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1998:729  HCAPLUS
DOCUMENT NUMBER:          128:88685
TITLE:                    Metathesis vs metastasis: the chemistry and biology of
                          the epothilones
AUTHOR(S):                Finlay, Ray
CORPORATE SOURCE:         Dep. Chemistry, The Skaggs Inst. for Chemical Biol.,
                          The Scripps Res. Inst., La Jolls, CA, 92037, USA
SOURCE:                   Chemistry & Industry (London) (1997), (24), 991-996
                          CODEN: CHINAG; ISSN: 0009-3068
PUBLISHER:                Society of Chemical Industry
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 15 refs. on a recent entry onto the scene of potentially
     useful natural products, the epothilones A - E, providing valuable
     information for the fight against cancer via their interaction with
     microtubules.
CC   26-0 (Biomolecules and Their Synthetic Analogs)
     Section cross-reference(s): 1
IT   Antitumor agents
     Stereoselective synthesis
        (chemical and bioactivity of the epothilones)
IT   Antitumor agents
        (metastasis; chemical and bioactivity of the epothilones)
IT   152044-53-6P, Epothilone A 152044-54-7P, Epothilone B
     186692-73-9P, Epothilone C   189453-10-9P, Epothilone D   201049-37-8P
     RL: BAC (Biological activity or effector, except adverse); BOC
     (Biological occurrence); BSU (Biological study, unclassified); SPN
     (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
     study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
        (chemical and bioactivity of the epothilones)
IT   152044-54-7P, Epothilone B
     RL: BAC (Biological activity or effector, except adverse); BOC
     (Biological occurrence); BSU (Biological study, unclassified); SPN
     (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
     study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
        (chemical and bioactivity of the epothilones)
RN   152044-54-7  HCAPLUS
CN   4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-
     8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-
     , (1S,3S,7S,10R,11S,12S,16R)- (9CI)  (CA INDEX NAME)

Absolute stereochemistry.  Rotation (-).
Double bond geometry as shown.
```



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:455072 HCAPLUS
DOCUMENT NUMBER: 127:156078
TITLE: Epothilones: novel microtubule-stabilizing agents
AUTHOR(S): Bollag, Daniel M.
CORPORATE SOURCE: Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Expert Opinion on Investigational Drugs (1997), 6(7), 867-873
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 44 refs. The past few years have witnessed the regulatory approvals of the anticancer microtubule stabilizing taxane drugs, Taxol and Taxotere which are rapidly gaining acceptance as important antineoplastic agents with potential against numerous solid tumor malignancies. Despite a basic understanding of the biochem. target of taxanes dating back nearly 20 yr, new classes of tubulin-binding microtubule polymerization enhancers were only reported in the last two years. Epothilones and discodermolide are newly discovered compds., which are structurally distinct from the taxanes, but which possess similar tubulin polymerizing and cell biol. effects. In the first studies reported, these compds. displayed similar or greater potencies than taxanes, and the epothilones may represent an advance over the taxanes in retaining toxicity against various taxane-resistant cell lines. This review summarizes the data published on epothilones and discodermolide and proposes further steps that could establish these new classes of compds. as potential second generation microtubule polymerization enhancers.

CC 1-0 (Pharmacology)
IT **Antitumor agents**

Microtubule
(epothilones and discodermolide as novel microtubule-stabilizing agents in relation to anticancer activity in humans and laboratory animals)

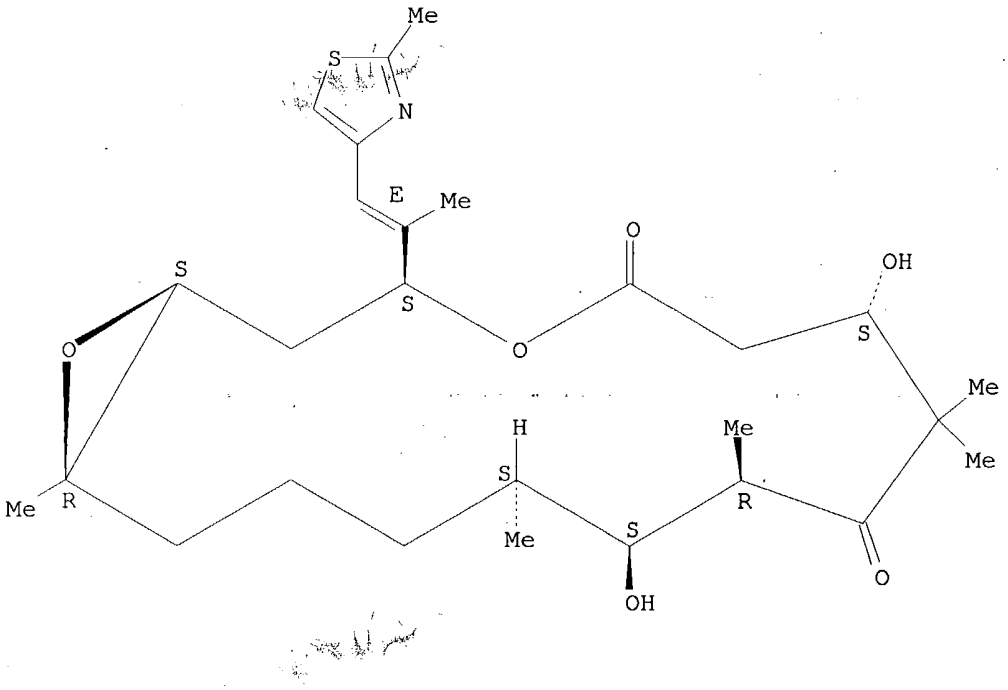
IT 127943-53-7, Discodermolide 152044-53-6, Epothilone A
152044-54-7, Epothilone B
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(epothilones and discodermolide as novel microtubule-stabilizing agents in relation to anticancer activity in humans and laboratory animals)

IT **152044-54-7**, Epothilone B
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(epothilones and discodermolide as novel microtubule-stabilizing agents in relation to anticancer activity in humans and laboratory animals)

RN 152044-54-7 HCAPLUS

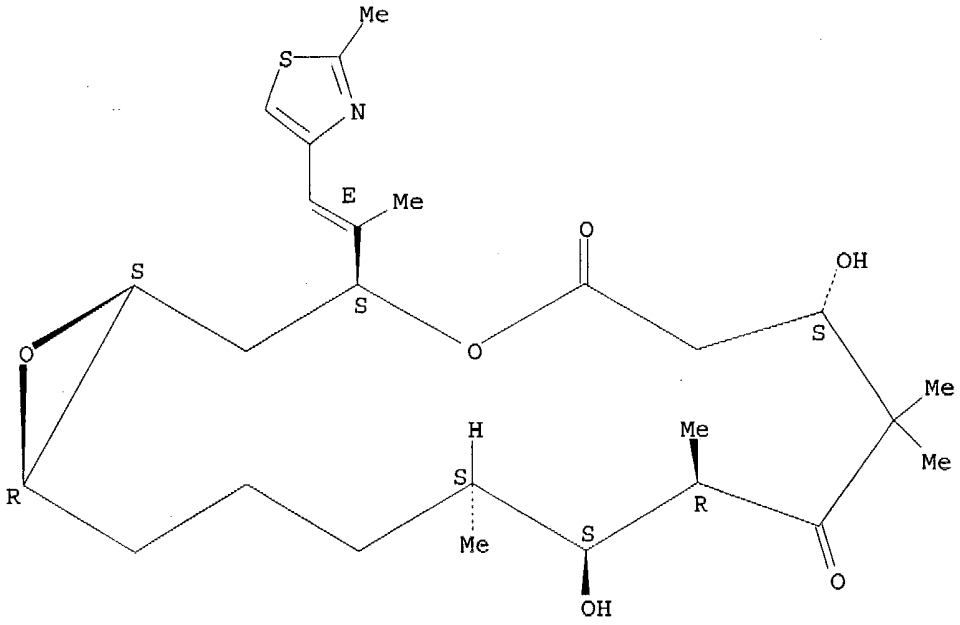
CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L28 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 152044-53-6 REGISTRY
CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-tetramethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-
OTHER NAMES:
CN (-)-Epothilone A
CN **Epothilone A**
FS STEREOSEARCH
DR 186692-57-9
MF C26 H39 N O6 S
SR CA
LC STN Files: ADISINSIGHT, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CEN, CIN, EMBASE, IMSDRUGNEWS, IMSRESEARCH, MRCK*, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); USES (Uses)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



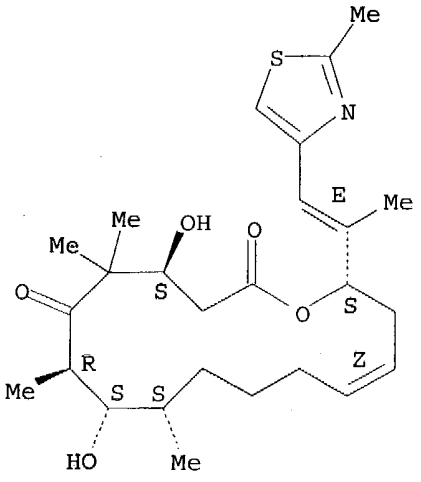
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

272 REFERENCES IN FILE CA (1907 TO DATE)
30 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
273 REFERENCES IN FILE CAPLUS (1907 TO DATE)

109 REFERENCES IN FILE CAPLUS (1907 TO DATE)

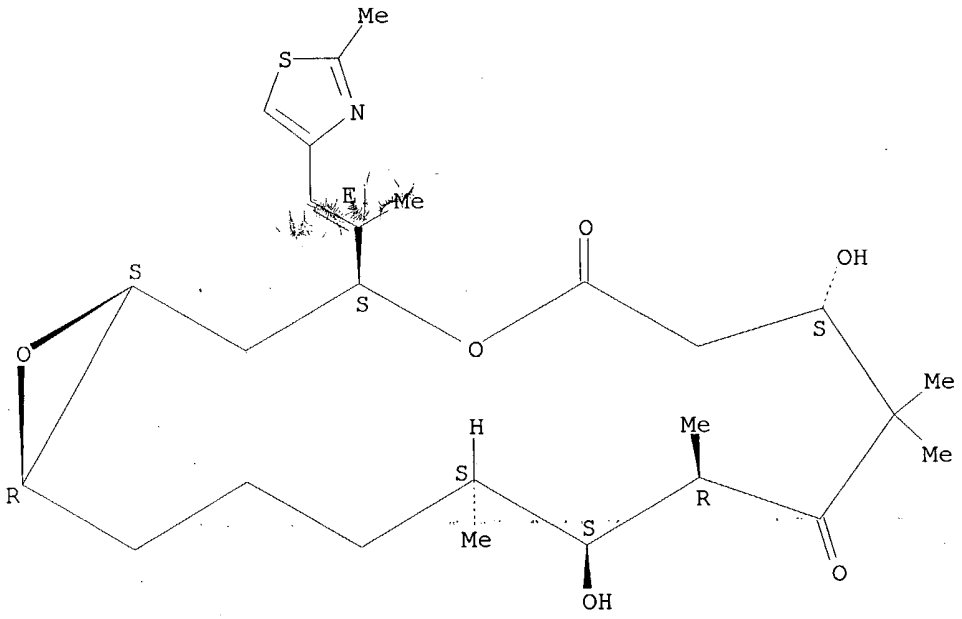
L34 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 186692-73-9 REGISTRY
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4S-[4R*,7S*,8R*,9R*,13Z,16R*(E)]]-
OTHER NAMES:
CN (-)-Deoxyepothilone A
CN (-)-Desoxyepothilone A
CN **Desoxyepothilone A**
CN Epo C
CN Epothilone C
FS STEREOSEARCH
MF C26 H39 N O5 S
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, IMSRESEARCH, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

109 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA


Me
S
N
E
Me
O
OH
S
S
O
O
S
Me
Me
H
Me
S
R
R
Me
S
O
OH

antineoplastic agents with potential against numerous solid tumor malignancies. Despite a basic understanding of the biochem. target of taxanes dating back nearly 20 yr, new classes of tubulin-binding microtubule polymerization enhancers were only reported in the last two years. Epothilones and discodermolide are newly discovered compds., which are structurally distinct from the taxanes, but which possess similar tubulin polymerizing and cell biol. effects. In the first studies reported, these compds. displayed similar or greater potencies than taxanes, and the epothilones may represent an advance over the taxanes in retaining toxicity against various taxane-resistant cell lines. This review summarizes the data published on epothilones and discodermolide and proposes further steps that could establish these new classes of compds. as potential second generation microtubule polymerization enhancers.

CC 1-0 (Pharmacology)

IT **Antitumor agents**
Microtubule
(epothilones and discodermolide as novel microtubule-stabilizing agents in relation to anticancer activity in humans and laboratory animals)

IT 127943-53-7, Discodermolide **152044-53-6**, Epothilone A
152044-54-7, Epothilone B
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(epothilones and discodermolide as novel microtubule-stabilizing agents in relation to anticancer activity in humans and laboratory animals)

IT **152044-53-6**, Epothilone A
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(epothilones and discodermolide as novel microtubule-stabilizing agents in relation to anticancer activity in humans and laboratory animals)

RN 152044-53-6 HCAPLUS

CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-tetramethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

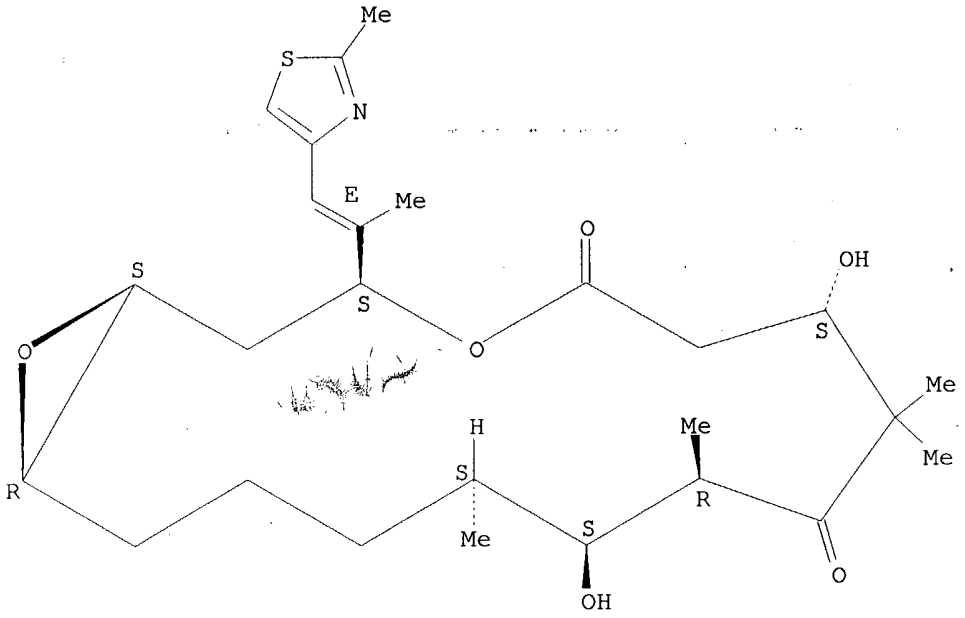
(chemical and bioactivity of the epothilones)

IT **152044-53-6P**, Epothilone A
RL: **BAC (Biological activity or effector, except adverse)**; BOC (Biological occurrence); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(chemical and bioactivity of the epothilones)

RN 152044-53-6 HCAPLUS

CN 4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-tetramethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

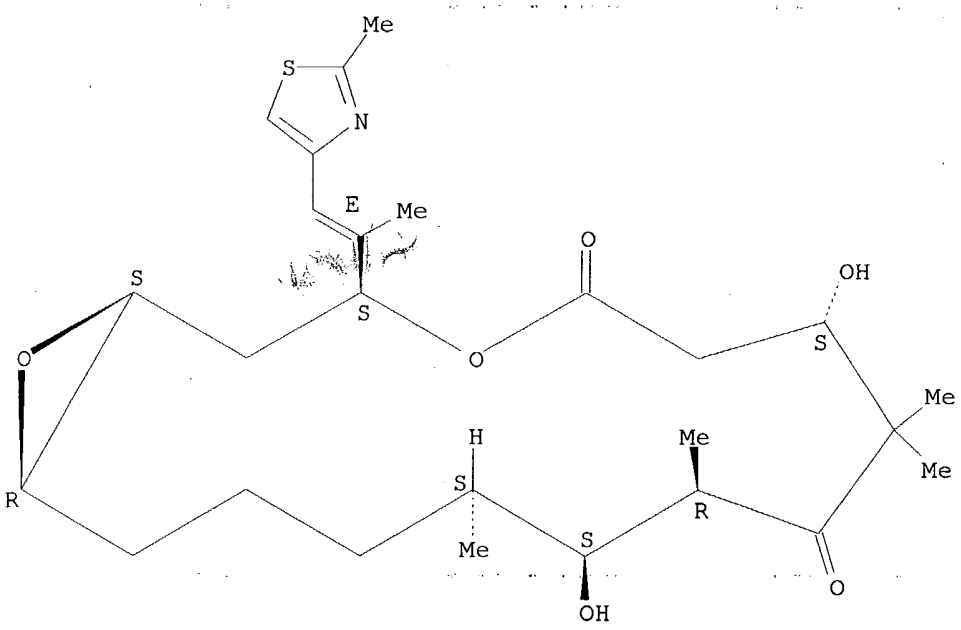


REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:455072 HCAPLUS
DOCUMENT NUMBER: 127:156078
TITLE: Epothilones: novel microtubule-stabilizing agents
AUTHOR(S): Bollag, Daniel M.
CORPORATE SOURCE: Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Expert Opinion on Investigational Drugs (1997), 6(7), 867-873
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 44 refs. The past few years have witnessed the regulatory approvals of the anticancer microtubule stabilizing taxane drugs, Taxol and Taxotere which are rapidly gaining acceptance as important

```
=> d que l67
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  EPOTHILONE A/CN
L30       178659 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTITUMOR AGENTS+OLD/CT
L66           98 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL AND L30
L67            3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L66 AND REVIEW/DT NOT PY>1997


=> d l67 ibib abs hitind hitstr 1-3

L67  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1998:69781  HCAPLUS
DOCUMENT NUMBER:          128:188181
TITLE:                    The use of microtubule poisons on tumor cells
AUTHOR(S):                Avila, J.
CORPORATE SOURCE:         Cent. Biol. Mol. Univ. Autonoma de Madrid, Madrid,
                          28049, Spain
SOURCE:                   Cancer Journal (1997), 10(6), 315-318
                          CODEN: CANJEI; ISSN: 0765-7846
PUBLISHER:                Association pour le Developpement de la Communication
                          Cancerologique
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A. review, with 20 refs.  It appears that the use of microtubule poisons
     is one of the most frequent therapeutic strategies for tumors.  Drugs like
     vinblastine and taxol have wide clin. use, although they have some
     drawbacks.  The discovery of new compds. such as epothilones could
     overcome some of the problems found with the use of earlier drugs.
CC   1-0 (Pharmacology)
IT   Antitumor agents
     Microtubule
        (use of microtubule poisons on tumor cells)
IT   64-86-8, Colchicine  865-21-4, Vinblastine  33069-62-4, Taxol
     152044-53-6, Epothilone A
     RL: BAC (Biological activity or effector, except adverse); BSU
     (Biological study, unclassified); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (use of microtubule poisons on tumor cells)
IT   152044-53-6, Epothilone A
     RL: BAC (Biological activity or effector, except adverse); BSU
     (Biological study, unclassified); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (use of microtubule poisons on tumor cells)
RN   152044-53-6  HCAPLUS
CN   4,17-Dioxabicyclo[14.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-
     tetramethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-,
     (1S,3S,7S,10R,11S,12S,16R)- (9CI)  (CA INDEX NAME)

Absolute stereochemistry.  Rotation (-).
Double bond geometry as shown.
```



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:729 HCAPLUS
DOCUMENT NUMBER: 128:88685
TITLE: Metathesis vs metastasis: the chemistry and biology of the epothilones
AUTHOR(S): Finlay, Ray
CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. for Chemical Biol., The Scripps Res. Inst., La Jolls, CA, 92037, USA
SOURCE: Chemistry & Industry (London) (1997), (24), 991-996
CODEN: CHINAG; ISSN: 0009-3068
PUBLISHER: Society of Chemical Industry
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 15 refs. on a recent entry onto the scene of potentially useful natural products, the epothilones A - E, providing valuable information for the fight against cancer via their interaction with microtubules.

CC 26-0 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1

IT **Antitumor agents**
Stereoselective synthesis
(chemical and bioactivity of the epothilones)

IT **Antitumor agents**
(metastasis; chemical and bioactivity of the epothilones)

IT **152044-53-6P**, Epothilone A 152044-54-7P, Epothilone B
186692-73-9P, Epothilone C 189453-10-9P, Epothilone D 201049-37-8P
RL: **BAC (Biological activity or effector, except adverse)**; BOC (Biological occurrence); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)